AMENDMENTS TO THE CLAIMS

Claims

1. (Currently Amended) ~~Method~~ A method for treating a crystal with a solution containing one ~~ore~~ or more molecule species, wherein the molecules have a molecular weight of < 500 Da, comprising the following steps:

   - fixing the crystal ~~is fixed~~ on a holding device, ~~in particular~~ without being embedded in a liquid environment~~,~~; and
   - applying microdrops of the ~~liquid~~solution ~~are applied~~ onto the crystal.

2. (Currently Amended) ~~Method~~ The method for treating a crystal according to claim 1, wherein the molecules contained in the solution have a molecular weight of < 200 Da.

3. (Currently Amended) ~~Method~~ The method for treating a crystal according to claim 1 ~~or 2~~, wherein the molecules contained in the solution have a molecular weight of < 100 Da.

4. (Currently Amended) ~~Method~~ The method for treating a crystal according to ~~any one of the preceding claims~~claim 1, wherein the crystal is a protein crystal.

5. (Currently Amended) ~~Method~~ The method for treating a crystal according to ~~any one of the preceding claims~~claim 4, wherein the molecules contained in the solution bind to the proteins in the protein crystal as ligands, preferably with an affinity between 10^{-3} and 10^{-4} M.

6. (Currently Amended) ~~Method~~ The method for treating a crystal according to ~~any one of the preceding claims~~claim 1, wherein the molecules contained in the solution or the molecules of at least one molecule species contained in the solution have at least one electron-rich or anomalous dispersion center, preferably a heavy(metal) atom.

7. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1, wherein ~~furthermore~~ a defined environment is generated around the crystal during the application of microdrops onto the crystal.

8. (Currently Amended) ~~Method~~ The method according to claim 7, wherein generating a defined environment comprises generating a gas stream of defined composition around the crystal.

9. (Currently Amended) ~~Method~~ The method according to claim 8, wherein the gas stream consists of an air stream with controlled air humidity.

10. (Currently Amended) ~~Method~~ The method according to claim 8, wherein the gas stream is regulated during the drip-on procedure.

11. (Currently Amended) ~~Method~~ The method according to ~~any one of claims 9 or 10~~claim 9, wherein the air humidity of the gas stream and the frequency, at which the drops are dripped onto the crystal by means of the micro dosage system, are synchronized during the drip-on procedure in such a way that the crystal is strained as little as possible and, in particular, that the volume of the crystal alters by no more than 20%, in particular by no more than 10%.

12. (Currently Amended) ~~Method~~ The method according to ~~any one of claims 8 to 11~~claim 8, wherein the gas stream comprises a solubilizer at a controlled concentration for a substance to be applied onto the crystal.

13. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 1 ~~to 12~~, wherein the volume of the microdrops is smaller than the volume of the crystal.

14. (Currently Amended) ~~Method~~ The method according to claim 13, wherein the microdrops of the solution have a volume of between 1 nl and 100 pl, preferably between 100 pl and 20 pl, and also preferably between 20 pl and 4 pl.

15. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1 ~~to 14~~, wherein the solution containing the molecule species and applied onto the crystal is an aqueous solution or a solution~~,~~ at least partially~~,~~ comprising organic solvents and, optionally, being heated up to more than 20°C.

16. (Currently Amended) ~~Method~~The method according to claim 15, wherein the solution containing the molecule species consists of or contains a volatile organic solvent.

17. (Currently Amended) ~~Method~~ The method according to claim 16, wherein the solvent consists of or contains DMSO.

18. (Currently Amended) ~~Method~~ The method according to claim 15 ~~or 16~~, wherein the solvent containing the molecule species is or contains a preferably entirely volatile organic solvent, which boils at a temperature of below 100°C.

19. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 15 ~~to 18~~, wherein the solvent contains DMSO, trifluoroethanol, acetone, chloroform, and/or methanol.

20. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1, wherein the molecules contained in the solution to be applied onto the crystal are hardly water-soluble.

21. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1, wherein the solution contains a cocktail of at least 3, more preferably at least 10, even more preferably at least 20, and most preferably at least 50 different molecule species.

22. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1, wherein the solution contains at least one molecule species at a concentration of 10^{-1} to 10^{-3} M.

23. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1, ~~wherein~~ further comprising, ~~a method step is inserted~~ before ~~the method~~the mixing and applying steps, ~~by means of which~~ a step of identifying fragments that potentially ~~binding~~ bind to a target structure ~~are identified, in particular a method step, which is based on~~using a spectroscopic method~~, for example NMR spectroscopy or surface plasmon resonance spectroscopy,~~ or an in silico docking method.

24. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 1 ~~to 23~~, wherein the gas stream contains one or more substance~~/~~s, which contain~~/~~s one or more ligand~~/~~s and/or inhibitor~~/~~s.

25. (Currently Amended) ~~Method~~ A method for determining a crystallographic structure of a complex ~~of, for example, a protein and at least one molecule species~~, ~~wherein~~ comprising (a) conducting the method steps according to ~~any one of claims~~claim 1 ~~to 24 are conducted~~, (b) irradiating the crystal ~~is irradiated~~ with X-ray or synchrotron radiation, and (c) recording the diffraction image of the crystal ~~is recorded~~.

26. (Currently Amended) ~~Method~~ The method for determining a crystallographic structure according to claim 25, ~~wherein~~ further comprising (d) calculating an electron density map ~~is calculated by means of~~ using the phase information and the intensity of the reflexes in the diffraction image and determining the binding site and positioning of the at least one bound molecule species ~~is determined, for example, in the protein structure~~.

27. (Currently Amended) ~~Method~~ The method according to claim 26, wherein the phase information is obtained ~~by means of the use of~~using heavy metal atom derivatives

("isomorphous replacement"), "molecular replacement", or MAD (multiple anomalous scattering).

28. (Currently Amended) ~~Method~~The method for determining a crystallographic structure according to claim 26~~ or 27~~, wherein the binding site and positioning of the at least one bound molecule species in the~~, for example, protein~~ structure is determined from the difference of electron densities of non-complexed and complexed structure by means of a electron density difference map.

29. (Currently Amended) ~~Method~~ The method according to~~ any one of claims~~claim 25~~ to 27~~, wherein the irradiation is conducted with monochromatic X-ray radiation or with synchrotron radiation during the treatment of the crystal with the solution.

30. (Currently Amended) ~~Method~~ A method for identifying molecules binding a crystallized protein, wherein (a) at least one molecule species is applied onto the crystal according to ~~a~~ the method according to ~~any one of claims~~claim 1~~ to 24~~, (b) diffraction intensities are measured at intervals of variable length, and (c) said diffraction intensities measured at intervals are compared with respect to their time-dependent sequence.

31. (Currently Amended) ~~Method~~ A method for identifying ~~of~~ a ligand binding ~~the~~ a target structure, ~~wherein~~ comprising (a) ~~a method according to any one of claims 1 to 24 is conducted, (b)~~determining the structure of at least one complex having at least two fragments ~~is determined~~ according to ~~a~~ the method according to ~~any one of claims~~claim 25~~ to 29~~, ~~(c)~~(b) determining at least one linker~~/s~~ to a ligand, which is~~/are~~ located between the at least two fragments~~, is/are determined~~, and ~~(d)~~(c) synthesizing a ligand containing the at least two fragments and the at least one linker ~~is synthesized~~.

32. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 1~~ to 24~~, wherein the method is conducted ~~by means of~~ using a device for treating a crystal with a substance having a holder for fixing the crystal and at least one micro dosage system, which

is arranged in relation to the holder in such a way that it can apply microdrops of the liquid onto the crystal fixed in the holder.

33. (Currently Amended) ~~Method~~ The method according to claim 32, wherein the device used according to the method furthermore comprises a device~~, by means of which~~ capable of generating a defined environment ~~can be generated~~ around the crystal during the drip-on procedure.

34. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 32 ~~or 33~~, wherein the device allows the generation of a defined environment by ~~means of~~ generating a gas stream of defined composition around the crystal.

35. (Currently Amended) ~~Method~~ The method according to claim ~~32 or~~ 34, wherein ~~furthermore~~ the holder is developed in such a way that the gas stream can be led through the holder in such a way that it is directed toward the crystal fixed in the holder.

36. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1, wherein a device having a holder consisting of a carrier block for a holder capillary, which has a free support end for the crystal, is used.

37. (Currently Amended) ~~Method~~ The method according to claim 36, wherein a device having a holder capillary consisting of a micropipette, in which a negative pressure can be generated in order to hold the crystal, is used.

38. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 36 ~~or 37~~, wherein the carrier block of the holder of the device ~~used in accordance with the present invention~~ has an integrated gas channel having a mouth end, which is directed toward the support end of the holder capillary.

39. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 34 ~~to 38~~, wherein a device is used, which ~~furthermore~~ has a gas mixing device~~, by means of which~~ capable of variably adjusting the composition of the gas stream ~~can be variably adjusted~~.

40. (Currently Amended) ~~Method~~ The method according to claim 39, wherein a device is used, in which the gas consists of air having a specific humidity content and the gas mixing device is ~~developed in such a way that by means of it~~capable of adjusting the air humidity ~~can be adjusted~~.

41. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 34 ~~to 40~~, wherein a device is used, which ~~furthermore~~ comprises a device for adding a solubilizer~~, by means of which~~ capable of adding to the gas stream a solubilizer for a substance to be introduced into the crystal structure of the crystal ~~can be added to the gas stream~~.

42. (Currently Amended) ~~Method~~ The method according to claim 41, wherein a device is used, which ~~furthermore~~ comprises a concentration adjusting device for adjusting the concentration of the solubilizer.

43. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 34 ~~to 42~~, wherein a device is used, which ~~furthermore~~ comprises a temperature regulating device capable of variably adjusting~~, by means of which~~ the temperature of the gas stream ~~can be variably adjusted~~.

44. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 32, wherein a device is used, in which the micro dosage system is developed in such a way that it can generate microdrops of the liquid to be applied onto the crystal, which have a volume that is smaller than the volume of the crystal.

45. (Currently Amended) ~~Method~~ The method according to claim 44, wherein a device is used, in which the micro dosage system is developed in such a way that it can generate

microdrops having a volume of between 10 and 20 percent of the volume of the crystal and preferably between 5 and 10 percent of the volume of the crystal.

46. (Currently Amended) ~~Method~~ The method according to ~~any one of claims~~claim 42 ~~or 43~~, wherein the micro dosage system is developed in such a way that it can generate microdrops having a volume of between 1 nl and 100 pl, preferably between 100 pl and 20 pl, and also preferably between 20 pl and 4 pl.

47. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1, wherein a device is used, in which the micro dosage system ~~furthermore~~ has a liquid supply system~~, by means of which~~ capable of supplying different liquids to be dripped onto the crystal ~~can be supplied~~, to a drop generating part of the micro dosage system in a time-dependently controlled manner.

48. (Currently Amended) ~~Method~~ The method according to claim 47, wherein a device is used, in which the liquid supply system of the micro dosage system comprises an electrically controllable precision syringe and a duct system, with which the precision syringe can be connected, via electrically controllable valves, with different liquid supply containers and with the drop generating part of the micro dosage system in order to supply liquid for drop generation to the latter.

49. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1, wherein a device is used, in which the micro dosage system is developed in such a way that it comprises a piezo pipette, which forms the drop generating part.

50. (Currently Amended) ~~Method~~ The method according to ~~any one of the preceding claims~~claim 1, wherein the crystal is vapor-plated with solvent, in particular with organic solvent, by means of an evaporator.

51. (Currently Amended) ~~Method~~ A method for X-ray crystallographic structure determination at high throughput, ~~wherein~~ comprising (a) holding one or more ~~the~~ crystal~~/s is/are held~~ ready, preferably in a freely mounted manner, (b) applying microdrops of a solution containing~~, for example,~~ at least one ligand ~~are applied~~ onto the preferably freely mounted crystals, (c) storing the crystals treated according to ~~method~~ step (b) ~~are stored~~, and (d) examining the crystals ~~are examined~~ X-ray crystallographically.

52. (New) The method of Claim 23, wherein the spectroscopic method is NMR spectroscopy or suface plasmon resonance spectroscopy.